MODULATION OF GLIAL CELL FUNCTIONS BY ADENOSINE AND PHARMACOLOGICAL REINFORCEMENT

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Brain ischemia, thought to be an aggravating factor for the development of dementia, is known to cause an activation of microglial cells and astrocytes which may influence the generation of secondary nerve cell damage. There is accumulating evidence that a pathological alteration of the Ca^{2+}-dependent molecular signalling is involved in the activation of glial cells. The endogenous cell modulator adenosine influences the intracellular Ca^{2+} homeostasis by modulating transmembrane Ca^{2+} influx and the release of Ca^{2+} from intracellular stores. Applying the fluorescence imaging technique on cultured type 1 astrocytes, we found that the intracellular Ca^{2+} mobilization by metabotropic receptor activation is largely potentiated by nanomolar adenosine concentrations via an A1 receptor-mediated mechanism [1]. This suggests that an activation of the high affinity A1 receptors may contribute to the initiation of astrocyte reactions as previously observed after in vivo ischemia. A2 receptor and cAMP-linked adenosine actions are favored by the neuroprotective pharmacon propentofylline (PPF) which blocks adenosine uptake and elevates its extracellular concentration up to a level sufficient to activate the low affinity A2 receptors [2]. In vivo treatment with PPF blocked the ischemia-induced hyperplasia of astrocytes and interfered with the expression of characteristic surface properties in activated microglial cells. In gerbils, daily posttreatment with PPF, started 24 hours after 5 min ischemia (i.e. when microglia activation had been already initiated), depressed or even abolished the immunostaining of activated microglia by antibodies against the major histocompatibility complex 1 (OX18) and β-amyloid precursor protein as well as the recognition by antibodies contained in the CSF of Alzheimer patients [3]. In vitro, PPF depressed the free oxygen radical formation in microglia-derived macrophages [4] and interfered with the transformation of microglial cells into full blown macrophages. The findings raise the possibility that pathologically induced glial reactions and in particular the potentially neurotoxic properties of activated microglial cells may be suppressed by pharmacological shifting of the balance between A1 and A2 receptor-mediated adenosine actions.

REFERENCES

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